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HERBERT O. CALVERY

Department of Pharmacology, Food and Drug Administration, Washington, D. C.

See Page 324, Coal-Tar Products

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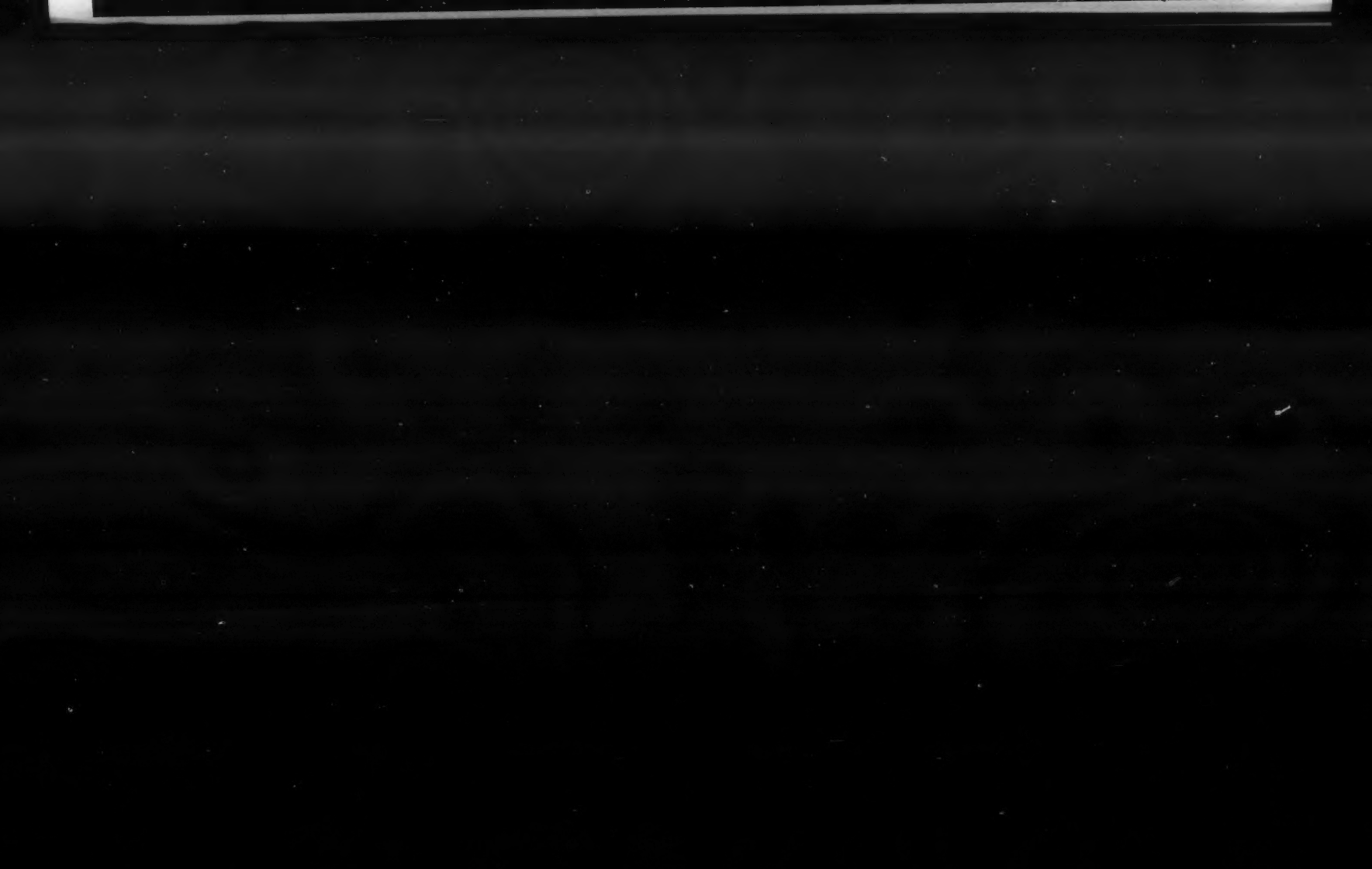

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1. J. A. M. A., 116:1342, March 29, 1941.
2. Zinsser, H., & Bayne-Jones, S.: A Textbook of Bacteriology, D. Appleton-Century Co., 1934.

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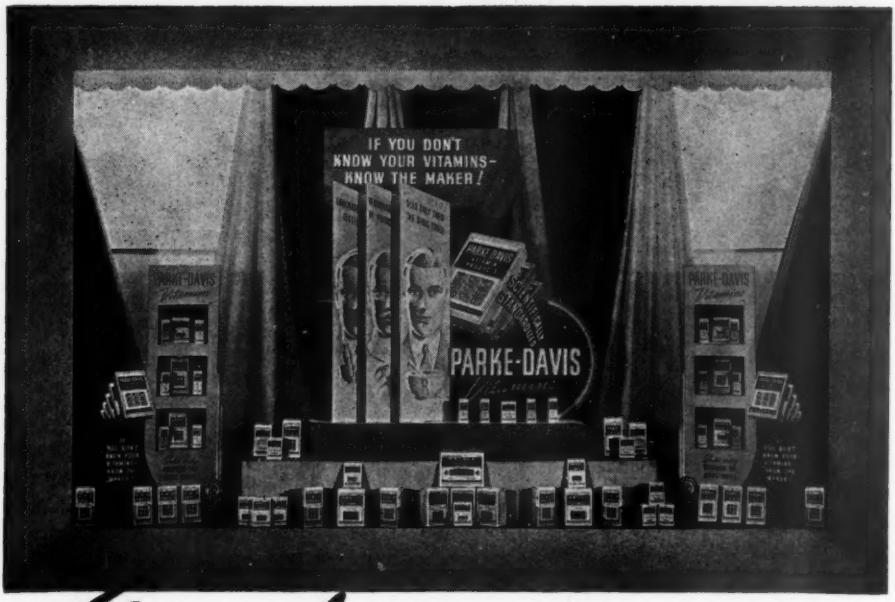

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CONTENTS

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EDITORIAL

AMERICA AND THE WAR

THAT this war will result in terrible casualties for the youth of our nation there can be little doubt. One of the worst features of war is, and ever has been, its insatiable appetite for youth. Thus there is cast a social and economic burden upon the post-war era by reason of the frightful expenditure of the energy and effort of millions of young men who may not be counted upon to share in the labor of reconstruction.

Likewise for those who for various reasons cannot serve in the armed forces there are and shall be untold casualties, hardships and sufferings. Modern war is indeed total war and there is not a single man, woman or child in any nation involved in this struggle whose life will not be greatly altered by the exigencies of total mobilization and its necessary sacrifices. Actually, it is quite likely that the misery and unhappiness of the aged will in many cases exceed that of the young since youth is quite compatible with change whereas there comes with age a very real aversion towards radical changes, so much so, that severe mental and even physical suffering may be the result.

Most persons will agree that the anxiety of mothers, fathers, wives and sweethearts for the safety of the departing soldier far exceeds the concern that he himself feels for his own safety. The mounting difficulties faced by men engaged in many civilian activities now curtailed by the war are causing many a hectic day and sleepless night in an attempt to "hold on" or convert to some other more essential type of work.

And yet not all of the results of this war will be bad. Victory itself must surely be worth the sacrifice otherwise it is doubtful that we should have so firmly dedicated ourselves to its achievement. But there shall be other gains coming out of the war. Scientific and technological advances will be greatly accelerated as the result. The demands for superior machines and implements of war have spurred

research in their development until discoveries and improvements in technic and design now take place at an almost unbelievable rate.

With all of these advances, however, the really important change that will be brought about is in the people of all nations and particularly our own.

In the last two decades great changes have taken place in the general philosophy of our people, particularly youth. The old homely virtues of honor, integrity and respect for one's fellowman coupled with a deep sense of responsibility have been replaced with the attitude of getting by with as little effort as possible, "the government owes me a living" and other evidences of slovenly thought and habits. This attitude has been largely aided and abetted by many older persons who were either starry-eyed idealists or those who encouraged this concept for political reasons.

In the stern realities of war only fundamental truths and virtues can survive and much of the sham and tinsel of yesterday will vanish.

People are becoming aware of their neighbors and learning that each is interdependent on the other. Gradually there is dawning the realization that the failure of any individual to do his part is reflected by a loss to each and every other person in society. The old system of pressure groups seeking special privileges is no longer condoned. We are in fact again becoming a responsible society such as that which founded this great country. The young men who are in the armed services when they return home on furlough surprise us. Gone are the signs of mental and physical flabbiness; they are strong and tough and indicate a real capacity for positive action. It is evident that those who survive this conflict may be counted upon as sound useful citizens of tomorrow.

American pharmacy is likewise being slowly but surely "toughened up" as it were. It, too, suffers from flabbiness in many places and the process cannot help but be painful. If it should emerge from this war occupying that proper place in the public health picture that all of us who respect it know it should then our sacrifice will not have been too great and our future indeed bright.

L. F. Tice.

COAL-TAR COLORS

Their Use in Foods, Drugs and Cosmetics

By Herbert O. Calvery

Division of Pharmacology, Food and Drug Administration, Washington, D. C.

THE use of colors in foods is a practice which has existed from ancient times. Obviously these colors, before the discovery of a method of synthesis of the so-called "aniline dyes," were restricted to those of animal, vegetable, or mineral origin. With the advent of synthetic coal-tar colors, their use in foods began immediately and was extended to drugs and cosmetics, first throughout continental Europe and then in America. The first concern of the United States Government with colors in foods was confined primarily to imports. The question, of course, was as to the harmlessness of the colors and whether or not their use resulted in deception as to the quality or identity of the food.

The use of coal-tar colors in foods in the United States was first legalized by an act of Congress, August 2, 1886, which authorized the addition of coloring matter to butter. The second legal recognition of the use of color was in the act of June 6, 1896, when Congress recognized coloring matter as a legitimate constituent of cheese.

The use of coloring matter was recognized by Congress as a problem which might affect the health of the nation (in the Appropriations Act of May 25, 1900 for the Department of Agriculture). Under the allocation of funds for the general expenses of the Bureau of Chemistry was included an item "To enable the Secretary of Agriculture to investigate the character of proposed food preservatives and *coloring matters,*[1] to determine their relation to digestion and health and to establish the principle which should guide their use. . . ."

Under this authority the Secretary of Agriculture issued several Food Inspection Decisions relating to the coloring of foods prior to the effective date of the Food and Drugs Act of 1906. For our purposes we need mention only three of these:

[1] All italics throughout the paper are introduced by the author.

F. I. D. 4 (3c), issued August 6, 1904, called the attention of importers to the fact that a food is considered adulterated "if it be colored, powdered or polished with intent to deceive or to make the article appear of a better quality than it really is." This was in reference to the authority of the Import Act of 1848,[2] the Act of Congress of July 1, 1902, prohibiting interstate shipment of "any dairy or food product which shall be falsely labeled or branded," and to the authority vested in the Secretary of Agriculture by the Appropriations Act.

F. I. D. 29, issued September 27, 1905, dealt particularly with fabricated foods of the confectionery class. This decision stated: "It has been customary to use harmless artificial colors in such foods in preparing them for consumption. Such colors are not calculated to deceive or mislead because the foods themselves do not represent any natural food product." Such products artificially colored were not required to be so labeled. However, this applied only to those candies which did not contain a natural substance possessing a color as, for example, chocolate. A label declaration would be required on imitation chocolate.

F. I. D. 39, issued May 1, 1906, related to preservatives and artificial colors in macaroni. It contained the first statement by the Department concerning a coal-tar color that is deleterious to health: "A small amount of coloring matter is frequently added to macaroni. This substance is held to be injurious to health and is so classed by laws of several European countries, especially Italy which has decreed that among other colors Martius Yellow (dinitro yellow, naphthol yellow, Manchester yellow, saffron yellow, and gold yellow) must not be used in the preparation of foods." Macaroni colored with Martius Yellow was therefore excluded from importation. This was the last Food Inspection Decision issued by the Department of Agri-

[2] "*Regulations of Food and Drug Imports and Exports.* The prevention of the importation of adulterated and spurious drugs and medicines received the attention of Congress early in the history of our country. On June 16, 1848, a law was enacted (9 Stat. L., 237) providing that 'all drugs, medicine, medicinal preparations including medicinal essential oils, and chemical preparations used wholly or in part as medicine, imported into the United States from abroad, shall, before passing the custom-house, be examined and appraised, as well in reference to their quality, purity, and fitness for medical purposes, as to their value and identity specified in the invoice.' It prohibited the importation of such drugs, medicines, and medicinal preparations as were found to be adulterated or deteriorated, and authorized the Secretary of the Treasury to appoint special examiners of drugs, medicines, etc. This act came under the jurisdiction of the Secretary of the Treasury, and is still in force."

culture, before the passage of the Food and Drugs Act of June 30, 1906.

In reviewing the history of attempts to obtain federal food and drugs legislation in the United States, it is interesting to note that many commentators have used approximately these words: "While most of the larger, well-established concerns manufacturing foods, drugs, and drinks favored such regulatory legislation, there was some opposition on the part of others, and much pressure was brought against the enactment of a pure food and drug law. Few manufacturers dared to oppose openly the provisions for the prevention of fraud in the preparation of foods and drugs, but there were many who strongly and persistently opposed any provisions for curbing the use of preservatives and coloring matter in foods." (Food, Drug and Insecticide Administration, Service Monographs of the U. S. Government No. 50, page 9. Institute for Government Research, 1928.) In the Food and Drugs Act of 1906 the Secretaries of the Treasury, of Agriculture, and of Commerce and Labor, were designated to draw up rules and regulations for the enforcement of the act. A commission composed of three persons, each representing one of the several departments, was appointed. They were H. W. Wiley, Chief of the Bureau of Chemistry, Department of Agriculture; James L. Gerry, Chief, Division of Customs, Treasury Department; and S. N. D. North, Director, Bureau of Census, Department of Commerce and Labor.

The Commission drew up a set of forty regulations but before submitting them to the secretaries for approval they held a public hearing in New York on September 17, 1906. They had expected to complete the hearing in one day. Actually there was a very large attendance and the hearing lasted five and one-half days. In their report they stated that "the chief points of discussion were the use of *colors* and preservatives in food products, the proper designation of the state in which the product was made, and the size of the letters required upon the labels for the words which must occur thereon in accordance with the provisions of the act. Nearly all the representations which were made before the Commission were to the effect that the colors and preservatives which were used in foods were harmless in the quantities employed. The makers and dealers in aniline dyes especially, and the users thereof, were of the opinion that these bodies, when properly guaranteed by the manufacturers as wholesome,

should be allowed." The manufacturers of confectionery introduced evidence to show that aniline dyes should not be excluded and another line of evidence was introduced to show that only vegetable colors should be used in butter.

The Food and Drugs Act of June 30, 1906, declared confectionery to be adulterated "If it contain terra alba, barytes, talc, *chrome yellow* or other mineral substance or *poisonous color* or flavor . . .". Any food was declared adulterated ". . . if it be mixed, *colored,* powdered, coated, or stained in a manner whereby damage or inferiority is concealed." Reference to harmless coloring also was made in the provisions on misbranding.

The Commission, in drawing up the regulations, referred to coloring matter as follows: "Only *harmless colors* or flavors shall be added to confectionery" (Regulation 10); "Only harmless colors may be used in food products" (Regulation 12); "*Coloring* and flavoring cannot be used for increasing the weight or bulk of a blend"; "In order that *colors* or flavors may not increase the volume or weight of a blend, they are not to be used in quantities exceeding 1 lb. to 800 lbs. of the blend"; "A *color* or flavor cannot be employed to imitate any natural product or any other product of recognized name or quality" (Regulation 21).

The first Food Inspection Decision on dyes after the effective date of the Food and Drugs Act on January 1, 1907, was F. I. D. 76, issued on July 13, 1907. In this decision it was stated "The use of any dye, harmless or otherwise, to color or stain a food in a manner whereby damage or inferiority is concealed is specifically prohibited by law. The use in food for any purpose of any mineral dye or any coal-tar dye, except those coal-tar dyes hereinafter listed, will be grounds for prosecution. Pending further investigations now under way and the announcement thereof, the coal-tar dyes hereinafter named, made specifically for use in foods, and which bear a guaranty from the manufacturer that they are free from subsidiary products and represent the actual substance the name of which they bear, may be used in foods. In every case a certificate that the dye in question has been tested by competent experts and found to be free from harmful constituents must be filed with the Secretary of Agriculture and approved by him.

"The following coal-tar dyes which may be used in this manner are given numbers, the numbers preceding the names referring to

the number of the dye in question as listed in A. G. Green's edition of the Schultz-Julius Systematic Survey of the Organic Coloring Matters, published in 1904.

"The list is as follows:

Red shades:

107. Amarynth
56. Ponceau 3 R
517. Erythrosin

Orange shade:

85. Orange I

Yellow shade:

4. Naphthol yellow S.

Green shade:

435. Light green S. F. yellowish

Blue shade:

692. Indigo disulfoacid

"Each of these colors shall be free from any coloring matter other than the one specified and shall not contain any contamination due to imperfect or incomplete manufacture." The rules for selection of these colors are discussed below. This decision was formulated by the Board of Food and Drug Inspection, which was created on April 25, 1907, by Order No. 11 of the Secretary of Agriculture. The Board consisted of H. W. Wiley, F. L. Dunlap, and G. P. McCabe. The Decision was approved as an amendment to the regulations by the Secretaries of Agriculture, Treasury, and Commerce and Labor.

In a memorandum accompanying this Food Inspection Decision detailed information was given concerning the selection of these seven colors. The need for the manufacturer's guarantee of purity was emphasized and it was stated: "It is the manufacturer above all who knows the exact nature of his dyestuffs, and if he is willing to sell his colors for use in foodstuffs he should be willing to guarantee that the dyes really are what they are represented to be, that they are not mixtures, and that they do not contain harmful impurities."

"In order further to minimize the possibility of harmful impurities existing in these dyes, it has been thought necessary to require a further examination by competent expert, a certificate from whom is necessary, stating that the dyes in question are what they are represented to be."

The first colors certified on April 1, 1908, were batches submitted by two different companies. These companies had spent thousands of dollars for equipment and personnel in order to manufacture colors of high purity for certification, but were unable to sell the colors at a profitable price. They were ridiculed by their competitors and stung by disappointment. Did F. I. D. 76 mean what it said? Although it was in reality an amendment to the regulations the government had no authority whereby it could enforce certification and could not bring prosecution unless there was evidence of actual violation of some section of the act by the use of uncertified colors.

F. I. D. 117, issued May 3, 1910, dealt further with the use of certified colors. It stated that certified dyes were on the market and might be used without objection if the dye did not conceal damage or inferiority, that uncertified colors are likely to contain arsenic and other poisonous material which might render the food injurious to health and therefore adulterated under the law, and further that if foods were found colored with dyes which contained either arsenic or other poisonous or deleterious ingredients which might render such foods injurious to health, the cases would be reported to the Department of Justice for prosecution. It also stated that certain vegetable colors might contain excessive quantities of arsenic, heavy metals and contaminations due to imperfect or incomplete manufacture but that there was no objection to the use of vegetable colors *per se*. This decision had the desired effect; the sale of certified coal-tar colors began immediately and soon reached substantial volume.

The manufacturers were not entirely satisfied with the original list of seven colors since they did not always impart the proper shade or were unstable under the conditions of use. To meet these requirements, new colors were added to the list from time to time. Naphthol Yellow S, Light Green SF Yellowish, and Indigo, were the least satisfactory of the group. Also there were no oil-soluble colors on the list and consequently uncertified colors were being used in fatty foods. The first color added to the list was Tartrazine, a yellow water-soluble dye added in 1916 (F. I. D. 164). The next were Sudan I, Butter Yellow (both subsequently withdrawn), Yellow AB and Yellow OB, all oil-soluble colors added in 1918 (F. I. D. 175). To supplement the green shade Guinea Green B was added in 1922 (F. I. D. 184), and Fast Green FCF in 1927 (F. I. D. 209). In 1929 Ponceau SX was added to the red shades and Sunset Yellow FCF to the

yellow shades (Service and Regulatory Announcement, Food and Drug No. 3, Supplement No. 1, April, 1929).

Although Indigo was an unsatisfactory blue for many purposes, it was not supplemented until September, 1929, when Brilliant Blue FCF was added (Service and Regulatory Announcement, Food and Drug No. 3, Supplement No. 2). This was the last of the coal-tar colors added to the permitted list of food dyes until after the Food, Drug, and Cosmetic Act of 1938 went into effect .

Selection and Rejection of Coal-Tar Colors Under the Act of 1906

The Department's concern over the use of coal-tar colors in foods antedated the Food and Drugs Act of 1906 by several years, as evidenced by the appointment of Dr. Bernard C. Hesse as an expert consultant on coal-tar colors. Dr. Hesse had had broad experience in this subject through long association with the leading dyestuff manufacturers in Germany. He made an extended study of the coal-tar dyes that were then in use for the coloring of foods and foodstuffs for the purpose of determining what restriction, if any, should be placed on their use. These investigations included not only a very detailed and exhaustive search of the literature concerning both the chemistry and physiology of these coal-tar colors and the laws of the various countries and states regarding their use, but included also many chemical examinations in his own and the Bureau of Chemistry's laboratories. The Department recognized the very efficient service rendered by Dr. Hesse by publishing in February, 1912, Bureau of Chemistry Bulletin No. 147, entitled "Coal-Tar Colors Used in Food Products." This publication is perhaps the most outstanding work of its kind. The rules laid down by Dr. Hesse as a guide to selecting colors for use in foods are:

RULE I: All colors which have not been physiologically tested either on man or animals shall not be permitted for use in foods.

RULE II: All colors which have been examined but with contradictory results shall not be permitted.

RULE III: All examined colors which were doubtful shall not be permitted.

RULE IV: Only those colors on the United States market in 1907 of definite composition which have been examined with favorable results shall be permitted.

At that time eighty different coal-tar colors were offered for the coloring of foods in the United States. Of these thirty had not been examined physiologically, twenty-six had been examined with contradictory results, eight had adverse reports, leaving only sixteen which could be considered with more or less certainty as harmless. A process of elimination was applied to these and nine were eliminated. Ten of the sixteen were red dyes of three classes of chemical structure. One of each class seemed to be required by the industry, therefore, on the basis of the number of requests Amarynth, Erythrosin, and Ponceau 3R were selected. There was only one orange and one blue, therefore, Orange I and Indigotine (Indigo disulphoacid) were both selected. There were two yellows which were tinctorially very similar. The choice of the industry was ten to one for Naphthol Yellow S; therefore, it was selected. Likewise, there were only two greens with little basis tinctorially for a choice between them. Therefore, on the basis of the number of requests by the industry, Light Green SF yellowish was the choice making a total of seven selected and nine rejected.

A search of the records of the Department has not revealed published requirements for the addition of new colors to the original permitted list of seven until the publication of S. R. A. F. D. No. 3 in October, 1927. Evidently Hesse's Rule I prevailed and those coal-tar colors subsequently added were all physiologically tested. This is indicated by the fact that following the addition of a new color to the list the Annual Reports of the Department usually mentioned the fact that after thorough physiological tests a certain color had been added.

The only colors that were added to the list and later removed by the Department were the oil-soluble Sudan I and Butter Yellow. The demand by the industry for oil-soluble yellow colors had continued from the beginning and increased in force. This demand undoubtedly stimulated the investigations of several oil-soluble colors by Salant and Bengis (J. Biol. Chem. *27*, 403, 1916). The dyes investigated included Sudan I, Butter Yellow, Yellow AB, and Yellow OB. They were administered subcutaneously, intraperitoneally, intravenously, and orally. The authors concluded that: "The toxicity of the different dyes was not pronounced even when large doses were administered." The Department recognized that Sudan I and Butter Yellow were not as satisfactory as Yellow AB and Yellow OB. Sudan I and Butter Yellow were included to forestall criticism on the ground

that listing but two colors would result in a trade advantage to the single firm then prepared to manufacture Yellow AB and Yellow OB. It was recognized, however, that none of these four colors were patented and all color manufacturers would be in a position to undertake their manufacture. Sudan I and Butter Yellow had been on the permitted list about six months before adverse effects were first reported to the Department. Workmen handling these two colors were attacked by a rash which began on the arms and later covered almost the entire body. There were no characteristic lesions noted and there was no evidence that the condition was due to an infection or that it was contagious. There were no reports of harmful effects on consumers of foods colored with these dyes. The condition was apparently a contact dermatitis occurring in some instances in as many as 90 per cent. of the employees in a single plant. The evidence pointed primarily to Butter Yellow as the offending agent. However, investigations in the Department's laboratories of the effect of these colors on the skin of animals indicated that Sudan I was a primary irritant and that Butter Yellow was not. The dermatitis affected the personnel not only of one but several manufacturing plants. Because all the evidence pointed to a contact dermatitis and there was no evidence of injury from consumption, the Department permitted the manufacturers to dispose of their stocks but on June 7, 1919, issued a decision (F. I. D. 180) striking Sudan I and Butter Yellow from the list with the following statement: "Sudan I and Butter Yellow have been found unsatisfactory in practical use for food coloring purposes and these colors therefore are withdrawn from the list of those which may be certified for use in foods."

The investigations carried out by Salant and Bengis included neither skin tests nor chronic feeding experiments. If they had suspected that skin tests would be significant they would have avoided a difficult situation for the Department. If they had carried out chronic toxicity studies, they would have been the first to learn from Butter Yellow (p-dimethyl-amino-azobenzene) of the carcinogenicity of a coal-tar color. At this point it should be strongly emphasized that since January, 1919, no p-dimethyl-amino-azobenzene (Butter Yellow, Color Index No. 19; Color Index published by the Society of Dyers and Colourists, 1924, Bradford, England) has been certified in the United States for use in foods, that it was certified for such purposes only for a period of about six months, that it was never

extensively used in drugs and cosmetics, that it was never certified for such purposes and that since 1939 it has not, to our knowledge, been used in any food, drug, or cosmetic. It should be further mentioned that the two yellow colors, Yellow AB and Yellow OB, are still being certified. Although they are sometimes incorrectly called "Butter Yellow," they do not have the adverse physiological effect of Butter Yellow.

In the voluntary and nonremunerative system of certification in effect under the Act of 1906, patented colors were not permitted to be certified, whereas, under the Act of 1938 where certification is compulsory and fees are charged patented colors cannot be excluded and several are among those listed.

The Listing and Certification of Coal-Tar Colors Under the Act of 1938

The Food, Drug, and Cosmetic Act of June 25, 1938, contains the requirement that only certified coal-tar colors may be used in foods, drugs, and cosmetics. The effective date of this provision was June 25, 1939. It was recognized that immediate action was necessary if adequate information was to be obtained to provide a basis for the listing and certification of coal-tar colors needed for use in these three great classes of commodities. The food manufacturers were not seriously concerned because of the voluntary certification procedure which was already in effect. The drug manufacturers were not disturbed since they realized that if the requirements of cosmetic manufacturers and food manufacturers were satisfied they could probably use the same colors. This was the first experience of cosmetic manufacturers with a regulatory statute of this nature, and because of the enormous number of coal-tar colors they were using, they were particularly concerned.

Conferences were arranged early in July, 1938, with food, drug, and cosmetic manufacturers and with the coal-tar color manufacturers, and continued through August and September. It was learned that although about 1500 different substances were represented as being used by drug and cosmetic manufacturers, there were only about 300 true entities in actual use. The figure 1500 arose because of the fact that in some instances the same substance was being sold under as many as 25 or 30 different names, even by a single manufacturer, to jobbers and drug and cosmetic manufacturers. The limited time available did not permit the investigation and examination

of even 300 of these compounds. In collaboration with technical members of the coal-tar color, drug, and cosmetic industries, a weeding-out process was begun based on (1) toxicity; (2) extent of use; (3) essential nature because of special properties; (4) duplication of shade; (5) stability, with particular reference as to whether or not they were light-fast, acid-fast, or alkali-fast; and (6) chemical purity. In several instances a coal-tar color was suggested for listing but investigation revealed no use of it in the industry. Some manufacturers of cosmetics were using certain coal-tar colors when far more suitable ones were available, not only from the standpoint of nontoxicity and purity but also from the standpoint of stability and suitability of shade. Very few of the coal-tar colors had been sufficiently investigated to eliminate them of the basis of toxicity. However, it is interesting to note that among those so eliminated were the only two coal-tar colors known to be capable of producing carcinogenic manifestations. These were actually being used occasionally in drugs and cosmetics but, of course, such use is now discontinued.

After the elimination of many colors on the basis of the above criteria, a notice was issued to Manufacturers and Dealers in Coal-Tar Dyes on September 16, 1938, asking them to submit under certain restricted conditions samples of a number of coal-tar colors. Some of these samples were soon received and chemical and pharmacological investigations of them were begun at once. This notice was of a preliminary nature and after plans had more nearly crystallized, a second notice was issued on October 6, 1938, to which was attached a list of 93 coal-tar colors, including the 15 certified food colors, and the manufacturers were requested to submit a sample of one pound of each of these. It was asked that these 93 compounds be chemical entities and not complex salts or mixtures, except that if they were acids, sodium and potassium salts were acceptable, or if they were basic, the chloride or sulfate would be acceptable. A certain degree of purity was specified. The manufacturers were also asked to submit structural formulæ for their dyes and adequate methods for chemical analysis to show that the compound was of the chemical structure indicated by the formula. Fortunately our pharmacological investigations of the fifteen colors on the certified food list and several others, some of which we had had under way for a period of over two years, had been sufficiently extensive to furnish us a basis of evalua-

tion of the new colors. These investigations, using different species of animals, had included: acute tests by oral and intraperitoneal administration; subacute feeding experiments incorporating low, medium, and high levels of the dyes in the diets (in some of these experiments the animals were permitted free access to food while in others the "paired feeding" technique was used; and chronic feeding experiments with different levels of the dyes in the diets.

In light of the early experience with Sudan I and Butter Yellow and in view of other considerations, it was immediately obvious that no new color, however essential it seemed to be, should be added to the list, even with a background of commercial use, until a variety of pharmacological data were available to show its relative toxicity and its harmlessness and suitability for use when compared with the well-known food colors.

Our investigations consisted of the determination of the acute oral toxicity on rats, the acute intraperitoneal toxicity on mice, and a minimum of sixty days subacute feeding experiments. In these experiments three levels of the dye were fed to different groups of rats, the highest level being sufficiently large in all cases to produce positive results. In addition we tested each of the colors for their effect on the skin of groups of guinea pigs by the technique Landsteiner and his co-workers used in their investigations of the ability of compounds to cause skin sensitization. They had found that the skin of the guinea pig responds to most chemical compounds in a very similar manner to that noted in man.

When the first hearings were held, February 6, 1939, on the proposed regulations for the listing and certification of coal-tar colors, we had completed tests on over 125 individual colors and had eliminated many of them on the basis of our physiological and chemical examinations. Some of these were eliminated for the following physiological reasons: they were very toxic when administered to the animal in acute and subacute doses; they were primary skin irritants; or they were very powerful skin sensitizing agents. Others were eliminated for the following chemical reasons: they were mixtures of two or more colors; methods were not adequate for determination of the pure dye and intermediates in the batch; or possible deleterious intermediates and impurities were in too high concentrations. In most instances there was a combination of two or more of the above reasons for not including a dye in the list. In the proposed

regulations the 15 original certified colors and 78 new ones were listed. From the accompanying charts it can be seen that there are three groups of colors listed: FD & C, D & C, and Ext. D & C. The FD & C colors are the only ones which may be certified for use in foods but may also be certified for use in all forms of drugs and cosmetics. There were 16 of these, 15 of which were being certified under the voluntary system of certification. The new one had been carefully studied, the investigations including chronic feeding experiments on different species of animals of more than two years duration. After similar investigations a seventeenth FD & C color has been added to the list. The D & C colors constitute a group of dyes on which sufficient work has been done to justify the opinion that they are harmless and suitable for use in drugs and cosmetics for internal use where they come in contact with mucous membranes or are ingested only occasionally but there is not sufficient evidence to justify their use in foods where they may be ingested daily by children as well as adults. The Ext. D & C colors constitute a group which, because of their oral toxicity, should not be certified for use in products which may be ingested. They are for use only in those products which are externally applied.

Under the Food, Drug, and Cosmetic Act, public hearings are required for obtaining evidence upon which regulations are based. Witnesses may be cross-examined by anyone, whether consumer, manufacturer, or other interested party, who has presented himself as such interested party. The first such hearing on coal-tar colors was held in Washington, February 6, 1939, when evidence was presented by members of the staff of the Food and Drug Administration concerning the purity and safety of these compounds. The testimony of scientists outside the Administration was also presented. The manufacturers presented evidence concerning the need for these colors and other evidence which they felt should be in the record. Witnesses from consumer organizations gave testimony and questioned other witnesses. Several similar hearings have since been held on amendments to the original regulations.

The regulations and each amendment have been published in Federal Registers subsequent to each of the hearings on which the regulation or amendment is based. The amended regulations were published in September, 1940, as Service and Regulatory Announcement, Food, Drug, and Cosmetic No. 3. This publication lists the

colors which may be certified and gives the chemical name of each and the specifications for its certification. It sets forth the forms required to accompany the samples submitted for certification and specifies the fees required for the listing of new colors and for the certification of individual batches.

Discussion and Comment

The Food and Drugs Act of 1906 contained no authority for the certification of coal-tar colors. The certification procedure was purely voluntary. It is interesting to note that in the early phase of the procedure the manufacturer merely presented a certificate of analysis and the Department issued a statement advising him *not that his product had been certified* but that a number was assigned for use on packages from the batch. Later, the Department in several publications authorized the Bureau of Chemistry and the Food and Drug Administration forthrightly "To certify coal-tar colors which meet the accompanying requirement for certification." Under this authorization, members of the staff of the Bureau of Chemistry or the Food and Drug Administration issued to manufacturers such statements as "The food colors specified below are hereby *certified* . . .".

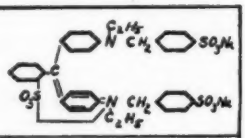
Prosecutions for failure to use certified colors could not be instituted unless the uncertified color introduced harmful impurities which might render the product injurious to health. Under the act of 1938 the use of an uncertified color in any food, drug, or cosmetic shipped in interstate commerce is forbidden.

The development of the system of certification for coal-tar colors was a precedent that laid the groundwork for other and more effective control measures. It was natural under the new law to continue this and expand to other fields. It was the forerunner of the present system of certification of coal-tar colors; under it were set the first tolerances for heavy metals; it was the first instance where responsibility was assumed by the Government for the validity of a manufactured article; it was the first instance where products were required to be tested pharmacologically before sale to the consumer; it antedated the Sea Food Inspection Amendment and undoubtedly had some influence as a precedent for it, as well as for the new drug sections of the Act of 1938. It had a very definite bearing and influence on the establishment of a system of certification for insulin through the amendment enacted late in 1941.

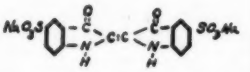
COAL-TAR COLORS LISTED FOR CERTIFICATION

F D & C Colors

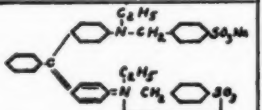
FD&C BLUE NO. 1
BRILLIANT BLUE FCF
CI. NO.



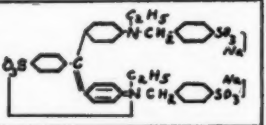
FD&C BLUE NO. 2
INDIGOTINE
CI. NO. 1180



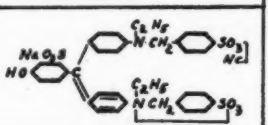
FD&C GREEN NO. 1
GUINEA GREEN B
CI. NO. 666



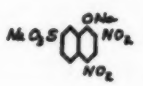
FD&C GREEN NO. 2
LIGHT GREEN SF YELLOWISH
CI. NO. 670



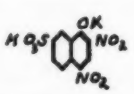
FD&C GREEN NO. 3
FAST GREEN FCF
CI. NO.



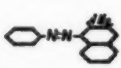
FD&C YELLOW NO. 1
NAPHTHOL YELLOW S
CI. NO. 10



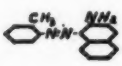
FD&C YELLOW NO. 2
NAPHTHOL YELLOW S-POTASSIUM SALT
CI. NO. 10



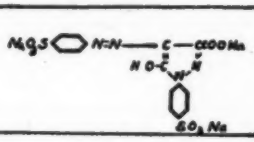
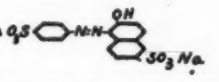
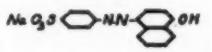
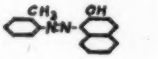
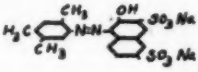
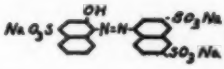
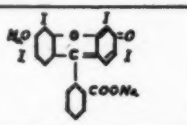
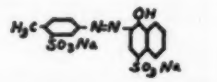
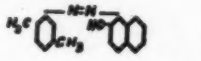
FD&C YELLOW NO. 3
YELLOW AB
CI. NO. 22



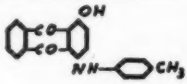
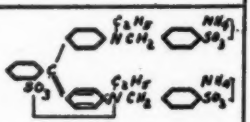
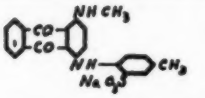
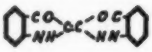
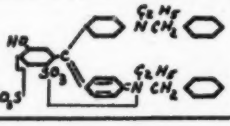
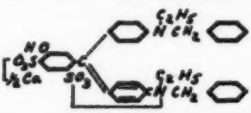
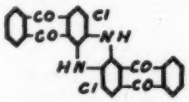
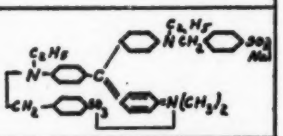
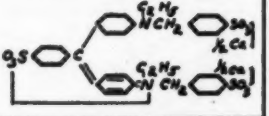
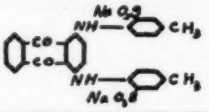
FD&C YELLOW NO. 4
YELLOW OB
CI. NO. 61



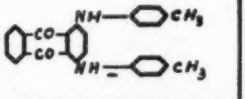
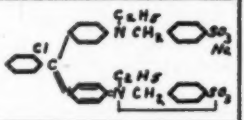
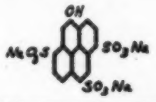
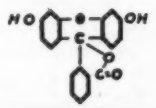
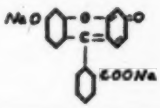
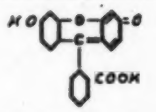
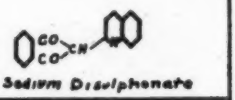
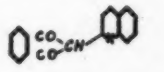
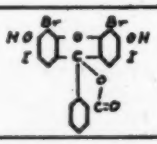
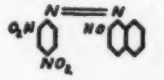
F D & C Colors (Cont.)

FD&C YELLOW NO. 5 TARTRAZINE CI. NO. 640	
FD&C YELLOW NO. 6 SUNSET YELLOW FCF CI. NO.	
FD&C ORANGE NO. 1 ORANGE I CI. NO. 150	
FD&C ORANGE NO. 2 ORANGE SS CI. NO.	
FD&C RED NO. 1 PONCEAU 3R CI. NO. 80	
FD&C RED NO. 2 AMARANTH CI. NO. 184	
FD&C RED NO. 3 ERYTHROSINE CI. NO. 773	
FD&C RED NO. 4 PONCEAU SX CI. NO.	
FD&C RED NO. 32 SUDAN MP, OIL RED XO CI. NO.	

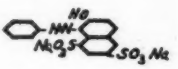
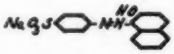
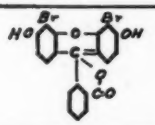
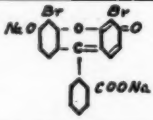
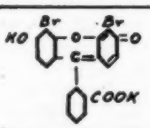
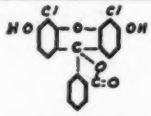
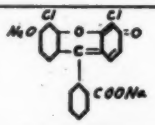
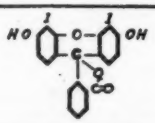
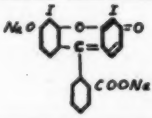
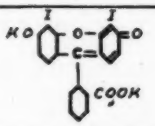
D & C Colors

D & C BLUE NO. 3 ALIZUROL PURPLE SS CI. NO.	
D & C BLUE NO. 4 ALPHAZURINE FG CI. NO. 671	
D & C BLUE NO. 5 ALIZARIN ASTROL B CI. NO. 1075	
D & C BLUE NO. 6 INDIGO CI. NO. 1177	
D & C BLUE NO. 7 PATENT BLUE NA BRILLIANT BLUE CI. NO. 714	
D & C BLUE NO. 8 PATENT BLUE CA CI. NO. 714	
D & C BLUE NO. 9 INDANTHRENE CI. NO. 1113	
D & C VIOLET NO. 1 WOOL VIOLET 5BN CI. NO. 697	
D & C GREEN NO. 4 LIGHT GREEN CF YELLOWISH CI. NO. 670	
D & C GREEN NO. 5 ALIZARIN CYANINE GREEN F CI. NO. 1078	

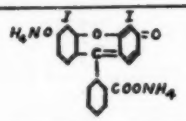
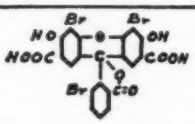
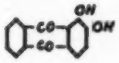
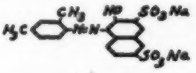
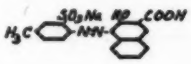
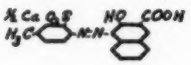
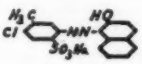
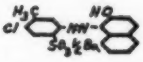
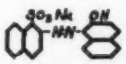
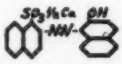
D & C Colors (Cont.)

D&C GREEN NO. 6 QUINIZARIN GREEN SS Cl. NO.	
D&C GREEN NO. 7 FAST ACID GREEN B Cl. NO. 667	
D&C GREEN NO. 8 PYRANINE Cl. NO.	
D&C YELLOW NO. 7 FLUORESCEIN Cl. NO. 766	
D&C YELLOW NO. 8 URANINE Cl. NO. 766	
D&C YELLOW NO. 9 URANINE K Cl. NO. 766	
D&C YELLOW NO. 10 QUINOLINE YELLOW WS Cl. NO. 801	 Di Sodium Disulphonate
D&C YELLOW NO. 11 QUINOLINE YELLOW SS Cl. NO. 800	
D&C ORANGE NO. 16 DIIODODIBROMO-FLUORESCEIN Cl. NO.	
D&C ORANGE NO. 17 PERMANENT ORANGE Cl. NO.	

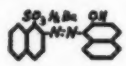
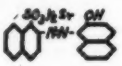
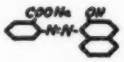
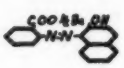
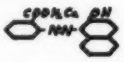
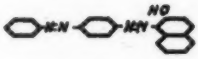
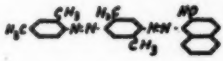
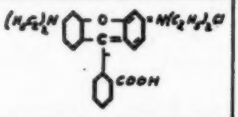
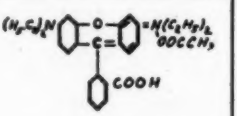
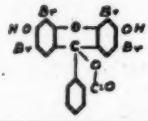
D & C Colors (Cont.)

D & C ORANGE NO. 3 ORANGE G CI. NO. 27	
D & C ORANGE NO. 4 ORANGE II CI. NO. 151	
D & C ORANGE NO. 5 DIBROMO-FLUORESCEIN CI. NO.	
D & C ORANGE NO. 6 DIBROMOFLUORES-CEIN NA CI. NO.	
D & C ORANGE NO. 7 DIBROMOFLUORES-CEIN K CI. NO.	
D & C ORANGE NO. 8 DICHLOROFLUORES-CEIN CI. NO.	
D & C ORANGE NO. 9 DICHLOROFLUORES-CEIN NA CI. NO.	
D & C ORANGE NO. 10 DIIODOFLUORES-CEIN CI. NO. 772	
D & C ORANGE NO. 11 ERYTHROSINE YELLOWISH NA CI. NO. 772	
D & C ORANGE NO. 12 ERYTHROSINE YELLOWISH K CI. NO. 772	

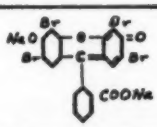
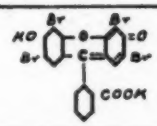
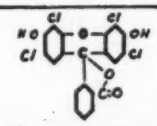
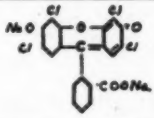
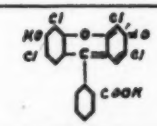
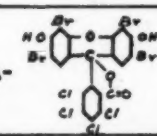
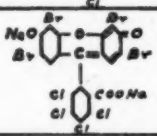
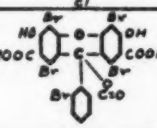
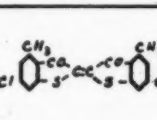
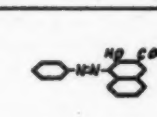
D & C Colors (Cont.)

D & C ORANGE NO. 13 ERYTHROSINE YELLOWISH NH CI. NO. 772	
D & C ORANGE NO. 14 ORANGE TR CI. NO.	
D & C ORANGE NO. 15 ALIZARIN CI. NO. 1027	
D & C RED NO. 5 PONCEAU 2R CI. NO. 79	
D & C RED NO. 6 LITHOL RUBIN B CI. NO. 163	
D & C RED NO. 7 LITHOL RUBIN BCA CI. NO. 163	
D & C RED NO. 8 LAKE RED C CI. NO. 185	
D & C RED NO. 9 LAKE RED CBA CI. NO. 185	
D & C RED NO. 10 LITHOL RED CI. NO. 189	
D & C RED NO. 11 LITHOL RED CA CI. NO. 189	

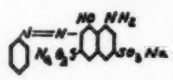
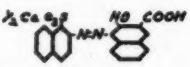
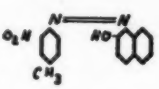
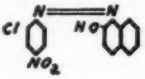
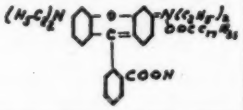
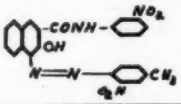
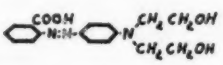
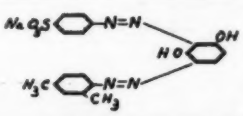
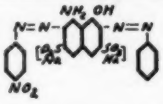
D & C Colors (Cont.)

D&C RED NO. 12 LITHOL RED BA CI. NO. 189	
D&C RED NO. 13 LITHOL RED SR CI. NO. 189	
D&C RED NO. 14 LAKE RED D CI. NO. 214	
D&C RED NO. 15 LAKE RED DBA CI. NO. 214	
D&C RED NO. 16 LAKE RED DCA CI. NO. 214	
D&C RED NO. 17 TONEY RED CI. NO. 248	
D&C RED NO. 18 OIL RED OS CI. NO.	
D&C RED NO. 19 RHODAMINE B CI. NO. 749	
D&C RED NO. 20 RHODAMINE B ACETATE CI. NO. 749	
D&C RED NO. 21 TETRABROMO-FLUORESCEIN CI. NO. 768	

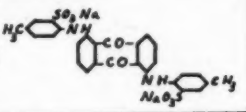
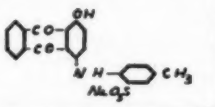
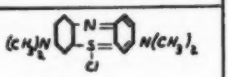
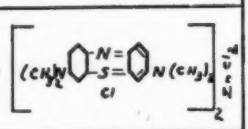
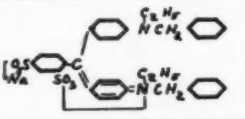
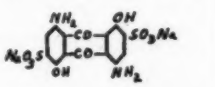
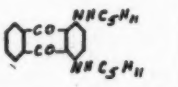
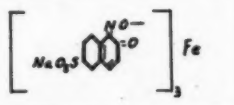
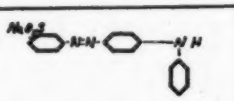
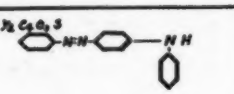
D & C Colors (Cont.)

D & C RED NO. 22 EOSIN YS CI. NO. 768	
D & C RED NO. 23 EOSIN YSK CI. NO. 768	
D & C RED NO. 24 TETRACHLORO-FLUORESCEIN CI. NO.	
D & C RED NO. 25 TETRACHLORO-FLUORESCEIN NA CI. NO.	
D & C RED NO. 26 TETRACHLORO-FLUORESCEIN K CI. NO	
D & C RED NO. 27 TETRACHLOROTETRA-BROMOFLUORESCEIN CI. NO. 778	
D & C RED NO. 28 PHLOXINE B CI. NO. 778	
D & C RED NO. 29 BLUISH ORANGE TR CI. NO.	
D & C RED NO. 30 HELINDONE PINK CN CI. NO.	
D & C RED NO. 31 BRILLIANT LAKE RED R CI. NO. 35	

D & C Colors (Cont.)

D&C RED NO. 33 ACID FUCHSIN D CI. NO. 30	
D&C RED NO. 34 DEEP MAROON CI. NO. 190	
D&C RED NO. 35 TOLUIDINE RED CI. NO. 69	
D&C RED NO. 36 FLAMING RED CI. NO.	
D&C RED NO. 37 RHODAMINE B STEARATE CI. NO. 749	
D&C RED NO. 38 TOLUIDINE MAROON CI. NO.	
D&C RED NO. 39 Z RED CI. NO.	
D&C BROWN NO. 1 RESORCIN BROWN CI. NO. 234	
D&C BLACK NO. 1 NAPHTHOL BLUE BLACK CI. NO. 246	

EXT D & C Colors

EXT D&C VIOLET NO. 1 ANTHRAQUINONE VIOLET B CI. NO. 1080	
EXT D&C VIOLET NO. 2 ALIZUROL PURPLE CI. NO. 1073	
EXT D&C BLUE NO. 1 METHYLENE BLUE CI. NO. 922	
EXT D&C BLUE NO. 2 METHYLENE BLUE-ZINC DICHLORIDE CI. NO. 922	
EXT D&C BLUE NO. 3 ERIOGLAUCINE X CI. NO. 673	
EXT D&C BLUE NO. 4 ALIZARIN SAPHIROL CI. NO. 1054	
EXT D&C BLUE NO. 5 HEXYL BLUE CI. NO.	
EXT D&C GREEN NO. 1 NAPHTHOL GREEN B CI. NO. 5	
EXT D&C YELLOW NO. 1 METANIL YELLOW CI. NO. 138	
EXT D&C YELLOW NO. 2 METANIL YELLOW CA CI. NO. 138	

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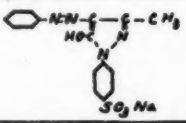
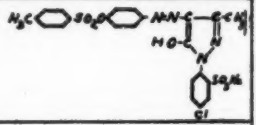
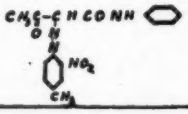
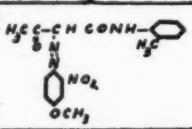
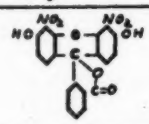
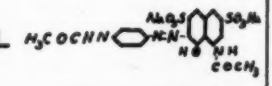
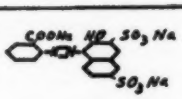
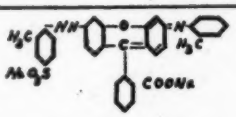
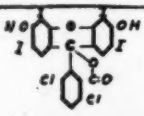
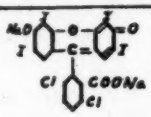
EXT D&C YELLOW NO. 3 FAST LIGHT YELLOW CI. NO. 636	
EXT D&C YELLOW NO. 4 POLAR YELLOW 5G CI. NO. 642	
EXT D&C YELLOW NO. 5 HANSA YELLOW CI. NO.	
EXT D&C ORANGE NO. 1 HANSA ORANGE CI. NO.	
EXT D&C ORANGE NO. 2 INDELIBLE ORANGE CI. NO.	
EXT D&C RED NO. 1 AMIDONAPHTHOL RED 6B CI. NO. 57	
EXT D&C RED NO. 2 PIGMENT SCARLET NA CI. NO. 216	
EXT D&C RED NO. 3 VIOLAMINE R CI. NO. 758	
EXT D&C RED NO. 4 DICHLOROTETRA-IODOFLUORESCEIN CI. NO. 777	
EXT D&C RED NO. 5 ROSE BENGALE TD CI. NO. 777	

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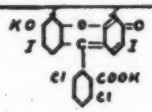
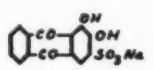
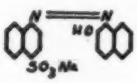
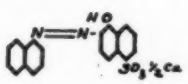
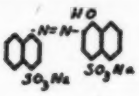
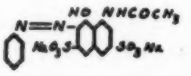
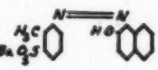
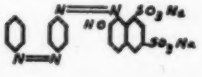
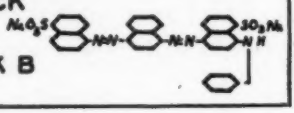
EXT D&C RED NO. 6 ROSE BENGALE TDK C.I. NO. 777	
EXT D&C RED NO. 7 ALIZARIN CARMINE C.I. NO. 1034	
EXT D&C RED NO. 8 FAST RED A C.I. NO. 176	
EXT D&C RED NO. 9 BORDEAUX RED C.I. NO. 84	
EXT D&C RED NO. 10 AZO RUBINE EXTRA C.I. NO. 179	
EXT D&C RED NO. 11 FAST CRIMSON GR C.I. NO. 31	
EXT D&C RED NO. 12 ROYAL SCARLET C.I. NO.	
EXT D&C RED NO. 13 CROCEINE SCARLET MOO C.I. NO. 252	
EXT D&C BLACK NO. 1 COOMASSIE FAST BLACK B C.I. NO. 307	

TOTAQUINE—ITS SOURCE, USES, AND REVISED U. S. P. XII STANDARDS

THE urgent need for quinine has aroused considerable interest in Totaquine which is essentially a mixture of alkaloids of varying composition obtained from cinchona bark. Totaquine was recognized in the U. S. P. XI by interim revision on June 10, 1942, but since that time a number of points have arisen requiring a decision based on fact. Consequently, a conference was held on this subject at Washington on September 1st, 1942, with the following results:

1. It was conclusively shown that Totaquine is of definite therapeutic value as an antimalarial.

2. The cinchona barks now available (chiefly from Central and South America) are exceedingly variable in alkaloidal content especially with respect to the per cent. of quinine as compared with cinchonine, cinchonidine and quinidine. No barks from these sources contain the high quinine content present in the cultivated barks formerly obtained from the East Indies and in fact many barks contain no quinine.

3. The average quinine content of barks containing quinine is 1-1.25 per cent.

4. Barks containing amounts of quinine in excess of 1 per cent. are needed for the production of quinine sulfate which is urgently required by the Army and Navy.

In view of the above facts the U. S. P. XII specifications for Totaquine were altered to read as follows:

Totaquine is a mixture of alkaloids from the bark of *Cinchona succirubra* Pavon and other suitable species of Cinchona. It contains not less than 7 per cent. and not more than 12 per cent. of anhydrous quinine, and a total of not less than 70 per cent. and not more than 80 per cent. of the anhydrous crystallizable cinchona alkaloids, the designation "crystallizable alkaloids" referring to cinchonidine, cinchonine, quinidine and quinine.

Totaquine of a higher quinine percentage may be reduced to the official quinine standard by admixture with Totaquine of a lower

percentage, or with any of the diluents permitted for powdered extracts under *Extracta,* providing the total anhydrous crystallizable cinchona alkaloids do not fall below the required percentage.

It was agreed that as soon as Totaquine meeting these specifications was commercially available an educational program should be instituted to encourage physicians to prescribe it as an antimalarial in place of quinine as a conservation measure. The drug industry is likewise to be notified in order that its use may be expedited by having it stocked in pharmacies and hospitals.

"SHRUNKEN FIGURE"

Since this Journal has carried editorials on the subject of a shortage of pharmacists the following editorial is reprinted from *Drug Topics.* It presents a new factor on the problem. (Ed.)

There has been much emotional nonsense spilled on both sides of the controversy over the actual or alleged shortage of registered pharmacists. Those who insist that there is no shortage have not hesitated to impugn the motives of those who insist that a shortage exists. Those who contend that the shortage is real, have little patience with the idealistic haze in which, so they emphasize, the theorists view the situation.

While the controversy has grown hotter and hotter, there have been those who saw the need for a cool-headed study of the problem.

Surveys have been made which seem to place the number of registered pharmacists on a much lower figure than that usually accepted.

For years we have been saying more or less glibly that there are "about" one hundred and ten thousand registered pharmacists. How this figure came to be on the tongue of everyone who discussed the subject is something of a mystery. But pharmacists quite generally looked upon themselves as constituting an army of about that size.

Now, investigations made by persons expertly qualified for such activities, have shown that the number of registered pharmacists actually occupied in the retail field does not exceed seventy-five

thousand. In other words, the body pharmaceutic is thirty-five thousand less than the popularly accepted estimate.

Instead of being a bloated, over-expanded profession, we find that pharmacy has become sharply, and perhaps, dangerously streamlined. Loose talk about what to do with too many will probably give way to an earnest attempt to get along with too few.

As a matter of fact, can seventy-five thousand pharmacists provide an adequate pharmaceutical service to both our armed and civilian-industrial populations? Can such a number of pharmacists provide a properly distributed pharmaceutical service and maintain it in conformity with the necessary public health standards?

These questions are a bit academic, because quite irrespective of what is demanded of them, serve they must, and serve they will.

We have no interest in the shortage controversy simply as a controversy, but we do feel that the time has come to deal with the subject on a factual basis, and do away with emotional, hysterical effusions which mean nothing and get nowhere.

IMPORTANT W. P. B. NOTICE

Chemicals and Drugs Listed as to Available Supply

IN a report dated August 21, 1942 certain materials and chemicals are listed by the W.P.B. on the basis of available supply. Group I contains those which are not available in sufficient amount for even essential civilian uses nor in some cases for war purposes alone. Group II lists those essential to the war industries but not as limited in supply as Group I. Group III lists those available in significant quantity as substitutes for scarcer materials. An abridged list of each group follows:

GROUP I

Acrylonitrile
Agar
Alcohol, Lauryl
Aluminum Trihydrate and Derivatives
Ammonia and Derivatives
Ammonium Cyanamide
Ammonium Sulphate
Anthraquinone Derivatives
Arsenic Trioxide
Benzol and Derivatives
Bleaching Powder
Butadiene
Butyl Alcohol
Calcium Cyanamide and Derivatives
Calcium Hypochlorite
Chlorosulphonic Acid
Cobalt Chemicals
Copper Chemicals
Cresols
Diphenylamine
Glycerol
Iron Oxide, Yellow Hydrated
Lithium Chemicals
Mannitol
Naphthalene and Derivatives
Naphthenic Acids and Derivatives
Nitric Acid
Oils:
  Cocoanut, Oiticica, Palm Kernel, Rapeseed, Sperm, Tung
Pentarythritol
Perchloric Acid
Phenol and Derivatives
Phosphates: Tricresyl, Triphenyl
Phthalic Anhydride and Derivatives
Pyrethrum
Quinine
Rotenone
Silica Gel
Sodium Nitrate
Sorbitol
Sulphur Chlorides
Toluol and Derivatives
Urea
Zinc Oxide (French)

GROUP II

Acetic Acid
Acetic Anhydride
Acetone
Alcohol: Amyl, Ethyl, Methyl
Acrylic Acid and Acrylates
Alkyd Resins
Aluminum Chemicals
Aniline and Derivatives
Antimony
Atebrine
Bismuth
Bromine
Butyl Acetates
Cellulose Nitrate
Chlorates and Perchlorates
Chlorinated Hydrocarbon Solvents and Waxes
Chlorine
Chromium Chemicals
Citric Acid
Ethers
Formaldehyde
Glycol
Iodine
Isopropanol
Ketones
Lactic Acid and Lactates
Maleic Acid and Anhydride
Manganese Chloride, Anhy.
Mercury
Molybdenum Chemicals
Nickel Chemicals
Paraffin Oils:
Babassu, Castor, Fish Liver, Linseed, Neatsfoot, Palm, Pine
Phosphorus
Phosphorus Oxychloride
Phosphorus Pentoxide
Potassium Permanganate
Silver
Strontium Salts
Vitamin A Products
Xylol

GROUP III

Aluminum Sulfate
Barium Carbonate
Bentonite
Borax and Boric Acid
Camphor
Casein
Caustic Soda
Charcoal
Chromic Acid
Muriatic Acid
Nicotine Sulfate
Oils:
Cottonseed, Peanut, Soybean, Sunflower Seed
Soda Ash
Sodium Silicates
Sodium Silicofluoride
Sodium Sulfide
Sulfur
Titanium Pigments
Turpentine
Zinc Oxide

RESEARCH SEEKS DOMESTIC PRODUCTION OF DRUGS CURTAILED BY WAR *

MORE than seventy-five persons employed by the Work Projects Administration of the Federal Works Agency are aiding Ohio State University staff members in research work directly connected with the present war emergency.

One phase of work which is of particular interest to the United States Department of Agriculture, is the production of drugs. Heretofore many of the drugs used for medicinal purposes were imported, but due to the war it has become almost impossible to obtain them. One common drug, belladonna, has increased in price about fifteen times its level of a year ago.

To find conditions under which these drugs thrive best, so that they may be produced profitably in Ohio, the Department of Horticulture has plants growing in experimental plots under almost every conceivable type of shelter and in all types of soil. Some of the plants are placed in inert material, such as gravel or ashes, and are fed different formulas of nutrient solutions so as to determine which elements are most conducive to their growth.

Employees of the WPA assist in the preparation of these experimental plots as well as care for the grounds and equipment and perform other related duties under supervision of the department's staff.

Speaking of WPA aid in regard to his particular department, J. H. Gourley, Chief of Horticulture, says, "We have at the present time several projects directly related to food and drug production and others that are closely related to both the food and fruit production program for the state. At the present moment I do not see where we could possibly secure assistance to carry this work forward without such labor as has been assigned to us recently by WPA. In addition to carrying on this food and drug production work, we have looked to this help for the preparation of our charts, graphs, and data for publication, and we have been particularly fortunate in having exceptionally good help along this line."

*From the Office of Information, Federal Works Agency, Washington, D. C.

SELECTED ABSTRACTS

From the Current Scientific Literature

The Use of Bulk Ether in Anesthesia. Harry Gold. *J. A. M. A. 120,* 44 (1942) No. 1. The hospital pharmacist is given further emphasis of the need and increasing demand for the use of bulk ether in anesthesia.

In 1934, studies proved that, with ordinary anesthetic ether cans which were opened many times and stoppered with cork, the contents remained pure for months according to very delicate chemical tests for the usual impurities, aldehydes and peroxides. This disproved the common belief that ether deteriorates quickly when the can is opened. Subsequent studies proved that cork stoppers did not promote oxidation of the ether, nor did the free access of air to the ether have any effect over a short period of time, there being no aldehydes or peroxides formed in either case.

Clinical tests at the New York Hospital and at other institutions proved that anesthetists could not distinguish the effect of ether from freshly opened small cans from that of ether from large drums which had been opened and stoppered with cork during periods of several weeks.

A survey made in 1941 disclosed that "all of the hospitals that are using bulk ether in five or thirty pound drums are satisfied that the quality of the ether is satisfactory."

The Twelfth Revision of the United States Pharmacopœia no longer considers ether unsatisfactory for anesthesia twenty-four hours after the container in which it is supplied is opened. The Pharmacopœia guards against the danger of transfer to containers that may not be suitable by directing that ether should not be used for anesthesia after it has been removed from the original container longer than twenty-four hours.

The need for the transfer of ether from large containers into smaller ones by the hospital pharmacist has focused attention on the fire and explosive hazard of the handling of ether, but then, almost every hospital pharmacy stocks ether, alcohol, acetone and gasoline

in bulk and repackages them in small containers to be distributed to the wards and laboratories for various uses.

The containers in which ether is issued to the operating room may be the tins in which anesthetic ether is supplied in commerce. They must first be thoroughly rinsed with the fresh ether with which they are to be filled. A special copper can may be made, and a reference to the source of such containers is given in this article. Complete references are also made as to the technique and materials needed for the transferal of bulk ether for anesthesia.

The safety of bulk ether for surgical anesthesia appears to be established. The danger of the transfer from large to small containers by the hospital pharmacist, if certain precautions are taken, is negligible. It has been proven that ether in five pound or thirty pound drums is practical only in institutions that use a considerable amount of ether, namely, those that have a weekly ether consumption of more than five or ten pounds. The financial saving is considerable —a hospital may reduce its ether for anesthesia bill by between 68 to 78 per cent.—a striking thought when it is realized that a million dollars' worth of ether was sold last year in small containers specially labeled for anesthesia. The wider application of this practice may be of particular importance in the present state of the nation, with the urgent need for economy in labor and in metal.

Irradiated Ergosterol Poisoning. P. A. Tumulty and J. E. Howard. *J. A. M. A. 119,* 233 (1942) No. 3. Recently there have been many clinical reports on the use of massive doses of vitamin D in the treatment of rickets, tetany, rheumatoid arthritis and various allergic states. Ill effects may follow the employment of massive doses of the vitamin; anorexia, loss of weight, nausea, vomiting, abdominal pain, diarrhea, muscular weakness, headaches, polyuria and polydipsia being significant indications.

In two observed cases the administration of repeated large doses of irradiated ergosterol was associated with a prolonged hypercalcemia and persistent impairment of renal function. The circumstances which may have contributed to this intoxication were the amount of drug which was given, the vehicle in which the drug was given, the calcium content of the diet, the factor of immobilization

and the season of the year. Hypercalcemia appears responsible for the renal damage manifested in these patients. The principle damage is thought to have occurred in the renal tubular epithelium. The functional impairment found in certain cases of sulfonamide nephritis is similar. Massive doses of irradiated ergosterol, at least under certain circumstances, present potential danger. A. Z.

Is an Optimum Diet or a Reduced Carbohydrate Intake Required to Arrest Dental Caries? R. O. Collins, A. L. Jensen and H. Becks. *J. A. D. A. 29,* 1169 (1942). At the 1940 meeting of the American Dental Association two views were expressed with regard to the prevention and control of dental caries by dietary measures. One viewpoint was that if an individual is in a normal physiologic state and adheres to a complete and optimum dietary program dental caries is prevented or controlled, while the other was to the effect that only by the reduction of the sugar content of the diet could this be accomplished.

In order to seek some clarification of these seemingly divergent opinions the authors have conducted a qualitative and quantitative analysis of the dietary intake of a group of caries-free individuals and a contrasting group with active caries.

No significant difference could be found in the nutritional adequacy of the individuals of either group and it appears doubtful that the caries incidence can be favorably influenced by increasing certain food elements so vigorously advocated by some.

The individuals were divided into two groups; those with no caries and no Lactobacilli in the mouth and those with caries and Lactobacilli. Their dietary evaluation showed no essential difference *except in the consumption of concentrated sweets.* The immune group averaged 10.5 teaspoonfuls of refined sugar and the caries-susceptible group almost twice this amount or 18.2 teaspoonfuls. A few individuals in each group were exceptions to this average finding, however, suggesting that carbohydrate consumption alone does not explain the absence or presence of dental caries in these cases and that other etiologic factors must be sought. A direct relationship does, nevertheless, exist between concentrated sweets; *L.*

acidophilus; caries. A reduced carbohydrate consumption therefore seems to be at least one means of decreasing the caries incidence and comes closer to the problem of dental caries prevention than present expressions of nutritional adequacy.

Phosphorus Burns. *Pharm. J. 95,* 53 (1942). Several references have been made in the daily press to the use by the Germans of incendiary bombs containing phosphorus. It appears that the contents of the bomb ignite spontaneously and often are scattered over a fairly large area. Phosphorus will only burn when it is dry and, in consequence, clothing and parts of the body on which pieces of phosphorus, or a solution of phosphorus, have lodged must be kept wet. The broadcast method of treating burns caused by phosphorus is to apply a solution of washing soda, about one tablespoonful to a pint of cold water, presumably to neutralize the oxy-acids that are formed, and to sponge liberally the part affected until all traces of phosphorus have been removed. As the composition of the material in the incendiary bomb is somewhat viscous, the phosphorus mixture may adhere tenaciously to the skin, in which event it should be removed with a dull knife or scrubbed with a nail-brush, the operation taking place under water, and a check made by examining the part affected in the dark in order to see whether all the phosphorus has been removed.

In instructions issued some time ago to Emergency Medical Services the following procedure was laid down by the Ministry of Health: (1) Immerse the affected part in water, or apply a thick pad soaked in water. (2) Remove particles of phosphorus embedded in the skin by means of gauze held in forceps, working under the water. (3) No oils or greasy dressings should be used. (4) Wash with dilute alkaline solution, e. g., sodium bicarbonate or sodium carbonate, 120 grains to a pint of water. (5) Remove all traces of phosphorus by washing with 1 per cent. solution of copper sulphate. (6) Remove the resultant dark deposit of copper phosphide and wash with a mild antiseptic, e. g., boric acid solution. (7) Apply a dressing as for ordinary burns.

The Detection of Lactose and Maltose by Means of Methylamine. W. R. Fearon. *Analyst 67,* 130 (1942). A new test for lactose or maltose is reported based on the reaction with methylamine in alkaline solution producing a bright violet-carmine color. The reaction is not given by polysaccharides, sucrose or any of the common monosaccharides. Neither is it given by any of the more obvious sugar decomposition products or related compounds including pyruvic, lactic, glyoxylic, acetic, citric, tartaric, mucic and ascorbic acids, glycerol, acetone, acetaldehyde, acetoacetic acid and diacetyl. It is also negative with proteins, fats and biological secretions such as saliva and urine. Other amines, namely, ethylamine and hydroxyethylamine, also produce the color reaction but higher amines both aliphatic and cyclic do not. The test is sensitive down to 0.05-0.1 per cent. lactose. It is recommended as a quick test for lactosuria and its differentiation from glycosuria and also to illustrate the hydrolysis of starch by acids, pancreatic juice or saliva.

The technic of the test is as follows:

Use a solution containing 0.1-1.0 per cent. of the sugar. To 4 cc. of the neutral solution add three or four drops of a 5 per cent. aqueous solution of methylamine hydrochloride. Boil the mixture for about thirty seconds. Remove the tube from the flame and at once add three to five drops of sodium hydroxide solution (20%). A yellow color appears, which slowly changes to carmine if lactose or maltose be present. If the mixture contains reducing sugars other than lactose the yellow color gradually deepens as in the familiar alkali test for sugars. In the absence of sufficient alkali the primary yellow color does not change to carmine so the amount added should be sufficient to raise the concentration of the mixture to 1-2 per cent. of sodium hydroxide. Once formed the amine pigment is stable for several hours and may be diluted ten to a hundred times with water for a rough colorimetric comparison. On acidification the color changes to yellow and is restored by addition of more alkali. It eventually fades on exposure to air but fading can be delayed by adding thiourea. Stronger reducing agents rapidly bleach the pigment.

Preparation of Barium Sulfate Suspensions. J. R. Elliott. *Pharm. J. 94,* 141 (1942). The preparation of a smooth suspension of barium sulfate is not such an easy procedure extemporaneously unless some suspending agent is employed. Tragacanth has been employed in this direction but it is now somewhat short in supply. The author reports excellent results using methyl cellulose as a suspending agent. A special grade certified as a "foodstuff quality" was employed and the medium viscosity type employed. The following procedure was adopted giving a 50 per cent. w/v suspension:

350 grains of the methyl cellulose is placed in a wide-mouthed bottle and sixteen fluidounces of water added. This is well shaken, left overnight, and finally stirred well the next morning. Two and a half pounds of barium sulfate is then rubbed down in a mortar with water until a smooth cream is obtained and to this the whole of the mucilage is added with further trituration. Suitable flavoring is then added and the whole made up to four pints with water. A smooth thickish white cream results and the solid remains well suspended.

Although methylcellulose is not subject to fungal attack it has no antiseptic properties and thus there is a possibility of a musty taste developing on long standing due to molds growing in the water or attacking the flavoring or sweetening agents added. This may be overcome by adding twenty grains of sodium benzoate to each four pints of the cream, a much smaller amount than is required in starch paste.

The Action of Mustard Gas on the Skin. G. B. Frost and H. M. Gelly. *Pharm. J. 95,* 70 (1942). No complete explanation has yet been given to account for the action of dichloroethyl sulfide on the skin. While it is well known that mustard gas possesses a delayed action these qualities are particularly marked where blistering is caused by prolonged contact with vapor concentrations. This substance is very soluble in animal fats, oils and lipids and as a result it penetrates deeply into the tissues of the body. Owing to the low resistance to penetration afforded by the ducts of the sweat glands and the hair follicles it is possible that these are penetrated rapidly while the epidermis is penetrated more slowly. The course

of the burning is somewhat as follows: The liquid takes from five to forty minutes for a 1 mm. drop to penetrate the skin; within two to six hours, or longer, an erythrematous blush appears. This slowly enlarges and within twenty-four hours either a large blister or a large number of small blisters results. These small blisters tend to coalesce. They usually burst within four days revealing a thin serous fluid and a raw surface underneath. A thin scab is formed and for small burns complete healing may be expected within one or two months.

It is possible that the hydrolysis of dichlorethyl sulfide to hydrochloric acid beneath the epidermis causes destruction of the unprotected tissues. It is suggested that the mustard gas when it has reached the layer of corium first reacts with the small quantities of moisture to form either a mixture of sulfonium chlorides and hydrochloric acid and thiodiglycol or it may react according to the following formula:

$$S\begin{matrix}\diagup CH_2CH_2Cl \\ \diagdown CH_2CH_2Cl\end{matrix} + HOH \rightleftharpoons S\begin{matrix}\diagup CH_2CH_2Cl \\ \diagdown CH_2CH_2OH\end{matrix} + HCl$$

A reaction of this type would undoubtedly account for the delayed action period since the action is balanced until water is in a considerable excess. As the vesicant comes in contact with more water the irreversible second phase of the hydrolysis would then take place.

$$S\begin{matrix}\diagup CH_2CH_2Cl \\ \diagdown CH_2CH_2OH\end{matrix} + HOH \rightarrow S\begin{matrix}\diagup CH_2CH_2OH \\ \diagdown CH_2CH_2OH\end{matrix} + HCl$$

A certain proportion of the dichloroethyl sulfide probably combines with proteins to form compounds similar to thiazanes. Albumin and globulin in the serum probably react in this manner; keratin in the epidermis and hair seems to be chemically unaffected.

The brown scar produced may be due to the slow hydrolytic decomposition of an addition compound possibly with tryptophane with the slow formation of melanogen which gradually oxidizes to a brown melanin compound.

Organic sulfur compounds are excreted through the skin especially the hands and feet for several weeks after blistering. These have a slight alliaceous odor even after washing.

The thicker the epidermal layer the slower the penetration, thus men with calloused hands are more suitable for decontamination work.

The authors give results of observation and treatment of experimental burns correlating several important factors determining severity and effectiveness of treatment.

Syrup Substitutes During War Time—*Chemist & Druggist, 133,* 318 (1940). Sugar shortages have made British investigators seek syrup substitutes for use as vehicles for various medicinal substances. Solutions of various gums have been studied and among them were the following two glycerin-containing mucilages which have retained their stability for four months or more at the time the report was written:

I. Gum tragacanth ..... 2 parts
Glycerin ..... a sufficient quantity
Water, q. s. to make ..... 100 parts

II. Karaya gum ..... 1 part
Glycerin ..... a sufficient quantity
Water, q. s. to make ..... 100 parts

In both these preparations, saccharin (0.1%) was used as a sweetening agent and methyl para-hydroxybenzoate (0.1%) as a preservative. The glycerin, it was stated, increases miscibility and forms a cream. In making these syrup substitutes, the mucilages should be brought to the boiling point, allowed to simmer for a half hour and then filtered through flannel.

SOLID EXTRACTS

Interesting—Readable—Pertinent

Municipal health boards are ever on the alert for unclean glasses and dishes in public eating places. Soon, however, they may need have no further worries about the transmission of disease through dirty dishes, for experiments are being conducted on a plastic substance which may be brushed or sprayed on glass, wood or metal, to form a germicidal coating on the utensil.

In the plastic under trial, a silver compound has been incorporated, affording a number of silver ions available on the surface of the coating to exert their germ-killing properties. As these are utilized, other ions come from the under portions of the plastic so that they, too, may maintain the germicidal action. This plastic is resistant to acids, alkalis and to normal wear and tear.

So far, only a limited group of bacteria have been killed in this manner, but the results have been promising. Work now is being done on pathogenic organisms.

AJP

Pennsylvania's first waterworks system was built in Schaefferstown, in Lebanon County, in 1736. The first pumping plant was built in Bethlehem, in 1754. A section of the original pipe indicates that the water was forced through hemlock logs, from eleven to twelve inches in diameter, with holes through the center measuring, roughly, six inches across. Despite the length of time these logs were in use, there seems to be no deposit on the interior.

AJP

After this present world conflict is over, pharmacists may justifiably point with pride to their patriotism, as evidenced by, among many other things, their purchase and sale of War Bonds and Stamps. Another striking evidence has been their response to the government's appeal for quinine stocks. Unopened packages have been pouring into the wholesale houses, and the Philadelphia College of Pharmacy and Science has, literally, been swamped with opened packages contributed by pharmacists throughout the country.

As noted in this journal last month, quinine, conchonine, quinidine and conchonidine, and their salts, are necessary for the pro-

tection of our armed forces in tropical areas. Every ounce counts, for quinine may now be considered ammunition. Wholesale houses are still receiving unopened packages of this drug and its derivatives, granting the donor full credit. The Philadelphia College of Pharmacy and Science, too, is still pooling stocks of opened packages, and further contributions are quite welcome.

AJP

Add one more achievement for science in this day of seeking substitutions or replacements for drugs formerly imported from abroad and now in demand by the armed forces. Atropine, from belladonna, now has a synthetic counterpart known as pavatrine, made from readily available substances. Commercial production will get under way soon.

AJP

It has been estimated that the synthetic rubber program will call for 100,000,000 pounds of soap a year. This soap is used in emulsifying butadiene, styrene and other ingredients prior to the polymerization process yielding the latex emulsion. Reclaiming processes also use soap as an essential step in converting old rubber into reclaimed latex emulsion.

AJP

Necessity is said to be the mother of invention. The tire shortage has led to the development of a "wrap around" tire covering. These are essentially a heavy cloth coated with an asphalt emulsion which can be wrapped around worn out tires. They will soon be released for sale.

AJP

The American Medical Association recently condemned a pamphlet distributed by the National Serological Society of Davenport, Iowa. According to this pamphlet, circularized to chiropractors, the system of compulsory vaccination is both dangerous and damaging to the health of both civilians and soldiers alike. This viewpoint is presumably that of the public relations director of the International Chiropractors Association.

It is strange indeed that in a country so enlightened in scientific matters that such malicious and unfounded statements are permitted to be distributed since they undermine public confidence and deter medical progress. The American Medical Association deserves praise for its forthright stand on this unfortunate incident.

BOOK REVIEWS

Two New Volumes Are Brought to Your Attention

The Pharmacopœia of the United States, Twelfth Decennial Revision. Mack Printing Company, Easton, Pa. $7.50.

The new United States Pharmacopœia is now on sale and its provisions and requirements become official November 1st, 1942. A considerable number of new drugs and preparations have been added with the view of making it an up-to-date and reliable therapeutic guide as well as a compilation of legal standards. The new preparations recognized were discussed in some detail in the June number of this journal.

The inclusion of a fairly representative number of dosage forms is considered to greatly increase the utility of the book to both the practitioner of medicine and the pharmacist and it should likewise increase the popularity of U. S. P. medication, particularly in prescription practice.

The policy of including in the price of the Pharmacopœia an amount sufficient to provide the purchaser with a bound supplement to appear in about two and one-half years will greatly increase the distribution of supplements. This was not apparently so well accomplished in the past.

When one critically examines the new book it is undoubtedly an excellent example of collaborative effort. Faults can be found in it by those who seek them with sufficient zeal but in general it is a tribute to the cooperation and understanding shown by the various groups represented on the Committee of Revision.

L. F. Tice

New Technical and Commercial Dictionary (Spanish-English, English-Spanish). By Antonio Perol Guerrero, Industrial Engineer, Escuela Central de Ingenieros, Madrid; Chief Editor, Editorial Técinca Unida, Brooklyn, N. Y. Over 50,000 Words, De Luxe Edition Thumb Indexed, Morocco Finish, Flexible Binding, Lettered in Gold, Full Tinted Edges. 1942. Chemical Publishing Co., Inc., 234 King St., Brooklyn, N. Y. Price: $10.00.

New words and arrangement of words are stressed in this new dictionary.

Many new names, approved by the Spanish Academy, particularly technical terms not found in most dictionaries, the result of discovery, invention, construction and war are found in this book.

An example of the arrangement of words illustrated by the word "Lathe." Lathe is found in the English section in the usual alphabetical order. Under lathe on separate lines appear forty-nine names of different lathes, each followed by the accepted Spanish name. "Bolt" and "Tank" have respectively forty-seven and twenty-six varieties listed.

Less than five minutes spent in looking up a few new technical or unusual words will prove the value of the "New Commercial and Technical Dictionary."

The arrangement of the words avoids the necessity of looking up many words in the other section of the book in order to find the word with the exact meaning desired.

The new words and the arrangement of the words used in this dictionary save time in writing clear concise letters and avoid delays due to misconceptions of terms.

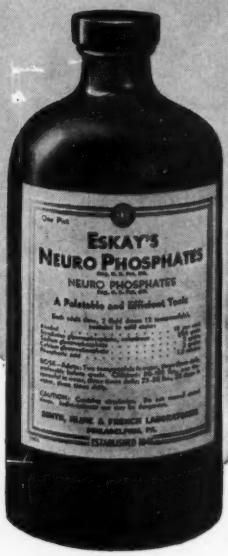
These advantages apply equally to translations from Spanish to English and from English to Spanish.

With the increasing importance of our relations with our South American neighbors, this dictionary should prove of very real value due to the more extensive use of Spanish in both scientific and commercial circles.

G. W. Patterson

TWO PALATABLE AND

Eskay's Neuro Phosphates



Each adult dose, 2 fluid drams (2 teaspoonfuls), contains in acid state:

Alcohol . . . . . 15 per cent

Strychnine glycerophosphate, anhydrous . . . . . 1/64 grain

Sodium glycerophosphate . 2 grains

Calcium glycerophosphate. 2 grains

Phosphoric acid . . . . 1.5 minims

This formula even on paper, instantly appeals to the physician as a judicious combination of recognized tonic ingredients. But the product itself is far more than a formula on paper.

Its scrupulous compounding, delicate balance, and outstanding appearance and palatability combine to give Eskay's Neuro Phosphates *an additional something*—a something which has been clinically proved.

Doctors have been prescribing Eskay's Neuro Phosphates for more than 30 years. *They prescribe it because it works.*

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EFFECTIVE TONICS . . .

Eskay's Theranates

The Formula of Eskay's Neuro Phosphates, plus Vitamin B_1

Each adult dose, 2 fluid drams (2 teaspoonfuls), contains in acid state:

Alcohol	15 per cent
Strychnine glycerophosphate, anhydrous	1/64 grain
Sodium glycerophosphate	2 grains
Calcium glycerophosphate	2 grains
Phosphoric acid	1.5 minims
VITAMIN B_1 (thiamine hydrochloride) (.75 mg.)	250 U.S.P. Units

and This formula answers the insistent demand by physicians for a second tonic, embodying the clinically proved formula of Eskay's Neuro Phosphates, *plus Vitamin B_1.*

Eskay's Theranates is not intended to replace Eskay's Neuro Phosphates. It is, rather, particularly indicated where the physician suspects a B_1 deficiency.

An exceptionally large quantity of Vitamin B_1 has been added to Eskay's Theranates—the equivalent, in adult dosage, of 750 U.S.P. Units daily.

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